Protocol for a Study of Nutritional Factors and the Low Risk of Colon Cancer in Southern Retirement Areas[1]

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Abstract

Colon cancer shows a distinct geographic pattern in the United States, with mortality rates in the Northeast exceeding those in the South by about 50%. The North-South gradient remains even after adjustment for differences in urbanization and socioeconomic status. Those counties in the South that attract large numbers of retirees from the North retain the low colon mortality rates characteristic of the South, even at older ages. This observation implies either that certain life-style changes associated with migration at retirement rapidly reduce the risk of colon cancer or that individuals migrate selectively, based on some correlate of health. A specific hypothesis related to the former possibility is that consumption of fruits and vegetables, and the associated vitamin C, carotene, and fiber, is elevated in the South and related to the reduced risk of colon cancer. A protocol is presented for a case-control interview study in Southern retirement areas to assess these possible explanations. A detailed residential history, as well as information on frequency of consumption of specific foods, food groups, and micronutrients, will be collected by interview and will be complemented by selected serum micronutrient determinations and fecal mutagenicity assays.

Rationale

Mortality from colon cancer shows a distinct geographic pattern in the United States, with high rates in the Northeast and low rates throughout the South (3). The North-South gradient is seen regardless of urbanization or socioeconomic level, with colon cancer rates in the Northeast exceeding those in the South by about 50% (Table 1). Several areas of the South, however, are populated with large numbers of migrants from the North. Counties in these areas also generally have low rates for colon cancer, even at older, retirement ages (Chart 1). Hence, it may be that some changes associated with moving South have reduced the risk of colon cancer. This decrease in risk stands in contrast to the increase observed among people migrating from countries at low risk of colon cancer, such as Japan, to countries at high risk, such as the United States (7).

Case-Control Study Protocol

A case-control interview study of colon cancer in Southern retirement areas is now being planned. Detailed information will be collected on diet and residential history plus data on drinking water source, anthropometry, marital and family history, medical history and drug use, occupational exposures, ethnicity, and other factors. Comparisons of the responses

between the cancer patients and controls will then be made, with particular attention paid to the times and places of origin of migration for those not born and raised in the South.

Failure to find differences in cancer risk according to the duration of residence in the South (as might be anticipated by the uniformity in mortality rates as a function of age in Southern retirement and non-retirement communities) would suggest that the risk reduction afforded by the Southern environment is conferred rapidly. Such a finding would imply that a series of events are necessary for eventual carcinogenesis after exposure to an initiator and that moving South lowers the likelihood of occurrence of the final event(s). Alternatively, the latent period between exposure to an initiator and appearance of clinical symptoms may be extremely short for colon cancer. It is also possible that individuals choosing to retire in the South are a self-selected group with less risk of dying from colon cancer. This possibility will be examined in a preliminary study focusing on residential history.

After the interviews have established the migration patterns of the cases and general population controls, the study will select a second control group. These will be adults from the counties of origin of those controls who had moved to the South. Comparable information will be sought so that the characteristics of migrants can be contrasted with the characteristics of those who remained in the North.

Dietary Survey

Although present and past dietary habits are difficult to quantify, the interview questionnaires will seek information on frequencies of consumption of certain foods. Limited information on food preparation (frozen-fresh-canned) and on cooking patterns will also be collected. Based on this input, nutrient intake will be estimated with United States Department of Agriculture food composition tables (18). An attempt will be made not to simply calculate total dietary fiber, which is an amorphous collection of several types of complex carbohydrates, but to utilize the conversion factors for cellulose, lignin, and other polysaccharide classes now being developed (16, 19). In asking about food frequencies and diet patterns, the respondent will be requested to focus on his adult life prior to the onset of clinical disease and to specify food consumption patterns that changed after migration.

The food frequency interview will evaluate current hypotheses about colon cancer etiology. Meat and fat consumption have been correlated with international variation in colon cancer rates (2). However, differences in meat and fat intake within the United States appear small (17). Therefore, the cause of the differential cancer risk between the North and the South may be related to differences in vitamin, fruit and vegetable, or fiber intake, any of which might interact with the heavy United States consumption of meat and fat. Thus, the study

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Table 1

Mean colon cancer mortality rates (per 100,000 population per year) in white males and females, from 1950 to 1969, according to geographic region, urbanization, and income[a]

Total population in county	Income level[b]	Geographic region						
		North-east	South-east	Mid-west	South Central	North Central	Moun-tain	Far West
		Males						
<75,000	Total	16.4	10.3	15.2	10.6	13.5	10.6	12.7
	Low	15.5	9.9	14.3	10.6	12.9	9.3	12.4
	Mid	16.0	10.2	15.4	10.3	13.8	10.9	13.6
	High	18.5	10.9	15.7	11.3	13.5	10.9	10.9
≥75,000	Total	19.2	12.7	17.5	12.1	15.9	12.3	13.7
	Low	17.5	10.7	17.0	10.3	15.4	10.9	12.1
	Mid	19.5	12.5	17.4	12.2	16.0	12.5	13.9
	High	20.3	15.2	18.5	13.8	16.4	13.2	15.1
		Females						
<75,000	Total	17.9	11.7	16.8	11.7	14.8	12.1	12.3
	Low	17.1	11.0	17.0	11.5	14.3	11.6	11.4
	Mid	18.0	11.8	16.7	11.6	15.0	11.7	12.1
	High	18.5	12.2	17.2	13.0	14.6	13.7	14.0
≥75,000	Total	19.0	12.8	17.0	12.3	15.9	12.5	13.5
	Low	18.8	11.5	17.4	10.4	15.8	11.0	13.2
	Mid	19.0	12.5	16.9	12.4	16.0	12.5	13.3
	High	19.2	15.3	16.8	13.9	15.6	13.5	14.5

[a] For additional information, see Ref. 3.

[b] Income levels are region and population specific. The "low"-income group comprises counties with median 1960 family income in the lowest 20% for all those counties in that region with population at that level. The "mid"-income group comprises counties in the mid-60% range; the "high"-income group comprises counties in the upper 20% range.

will attempt to uncover associations, positive or negative, of colon cancer with vitamins A, C, and E and selenium; carotene, green or yellow vegetables, meat, and vegetables in the genus *Brassica*; beef and other specific meats, broiled fish or meat, and dairy products; saturated fats, polyunsaturated fats, and cholesterol; dietary fiber, classes of complex carbohydrates, classes of fibrous fruits and vegetables, and whole grains. In analyzing the food frequency data, foods will be grouped (*a*) according to their content of a particular nutrient, like vitamin C or polyunsaturated fat; (*b*) according to traditional food categories, like meats, leafy green vegetables, or tubers; and (*c*) according to botanic nature, like *Brassica* (cabbage, cauliflower, broccoli), which contain the aromatic hydrocarbon hydroxylase-inducing indoles (10).

Serum Biochemistry

The study will also include a laboratory component to complement the dietary interviews. The cancer patients and both sets of controls will be asked at interview if they would be willing to have blood drawn by a staff nurse on a later visit and if they would be willing to collect stool specimens over an interval of several days. Biological specimens will then be obtained for systematic samples of the cases and controls; the size and characteristics of these samples will, in part, be based on interview responses.

The blood serum will be assayed for vitamin A, carotene, vitamin C, and vitamin E, for all of which there are reliable, standardized assays (6) and possibly for selenium. Vitamin A and carotene are of interest because of the traditional role of vitamin A in maintaining epithelium integrity, the ability of pharmacological levels of retinoids to inhibit tumor develop-

ment in animals (20), and the inverse association reported between vitamin A intake and lung (13) and bladder (12) cancer. Carotenoids are precursors of vitamin A, occurring in plants, and provide approximately one-half of the total vitamin A activity consumed. Serum carotene reflects recent intake of green leafy and yellow vegetables. However, serum vitamin A, controlled homeostatically by liver stores, reflects total vitamin A intake from animal and plant sources over a period of years.

Vitamin C is of interest because of its ability to reduce nitrites and prevent nitrosamine formation (14) and to protect vitamin A from oxidation. As a water-soluble, not a fat-soluble, vitamin, it is not stored in human tissues, and its serum levels are very sensitive to daily intake. Thus, repeat samples of blood, perhaps only enough for a microdetermination of vitamin C, would greatly improve the ability of serum vitamin C levels to characterize the typical vitamin C consumption of an individual. Vitamin E is of interest because of its ability to reduce nitrites and prevent nitrosamine formation (11), to inactivate free radicals formed from polyunsaturated fats, and to protect vitamin A from destruction. Since vitamin E is fat soluble, its levels in the serum are relatively stable and reflect intake over an extended period. Selenium deficiency has also been linked to colon cancer. A selenoenzyme appears to function as an antioxidant protecting cellular membranes and can compensate for vitamin E deficiency (and *vice versa*) (5). Assaying for still another micronutrient or two within the serum might be justified as a way to see if general vitamin-mineral deficiency is associated with colon cancer risk, and as a control.

Cholesterol and triglycerides and possibly some of the lipoprotein classes will be determined in the serum samples. Serum cholesterol is of interest because of the observation that colon cancer cases had, on the average, lowered cholesterol levels in the years prior to clinical onset of the disease (15). Polyun-
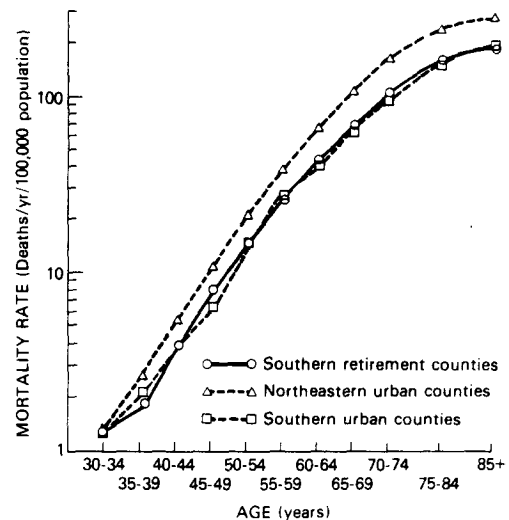

Chart 1. Colon cancer mortality, 1950 to 1969, among white male residents of Southern retirement communities compared to colon cancer mortality in other urban counties in the Northeast and in the South. The Southern retirement areas include Dade, Broward, Palm Beach, Hillsborough, and Pinellas counties in Florida; Maricopa and Pima counties in Arizona; and Los Angeles, Orange, and San Diego counties in California, all of which have populations exceeding 250,000. The other Southern urban counties include Guilford and Mecklenburg, N. C.; Greenville, S. C.; DeKalb and Fulton, Ga.; Jefferson and Mobile, Ala.; Caddo and Orleans, La.; Pulaski, Ark.; Dallas, Harris, and Tarrant, Tex., all of which have populations also exceeding 250,000. The Northern counties include all counties in the Northeast with populations exceeding 250,000.

saturated fats are known to reduce serum cholesterol and may perhaps be related to colon cancer induction. In any case, serum cholesterol, triglycerides, and limited lipoprotein data can serve to characterize fat metabolism within an individual.

Fecal Mutagen Analysis

Fecal samples will be collected from cases and both sets of controls primarily for mutagen analysis, although fractions of the fecal samples will be appropriately stored for later analysis of fiber components and bile acids and sterols, if deemed necessary. To reduce the notorious day-to-day variability in the mutagen activity of fecal samples from any one individual, feces will be collected for a period of several days, and combined. Mutagen analysis will utilize several standardized short-term tests that have already been tried on fecal samples and have detected mutagens: the Ames-*Salmonella* TA 100 assay for base pair substitutions (1); the Ames-*Salmonella* TA 98 assay for frame-shift mutations (1); and the *Escherichia coli* rec⁻ system (9). In studies with white and black South Africans (8), native and Hawaiian Japanese,[3] omnivorous and vegetarian Americans and rural Finns,[4] and individuals whose dietary intake of fiber, meat, and vitamins C and E was deliberately modified (4), these tests were able to detect a greater prevalence of strongly mutagenic fecal samples among the groups at higher colon cancer risk than among the groups at lower risk.

Analysis of the combined interview and laboratory data from this case-control study may help to evaluate the influence of nutritional and other factors on the geographic pattern of colon cancer in the United States.

Acknowledgments

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